

## Risk-Benefit Profile of Novel Anti-diabetic Drugs: Current Perspectives

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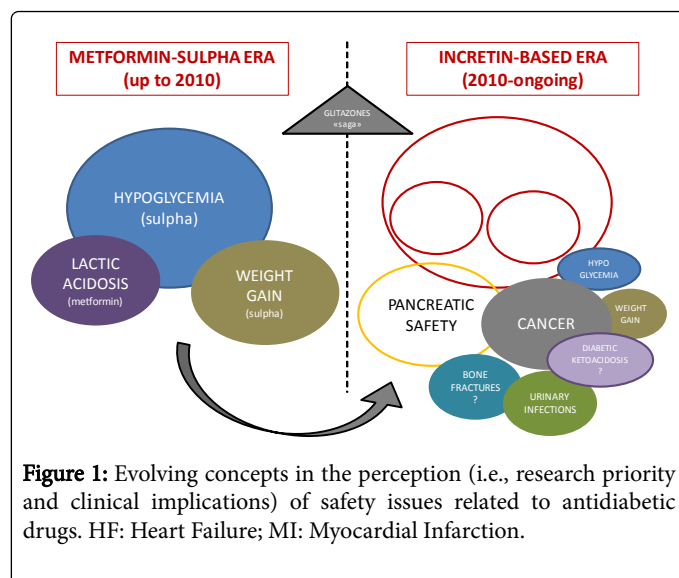
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Received date: July 14, 2016; Accepted date: July 27, 2016; Published date: August 05, 2016

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We are facing a paradigm shift in the era of antidiabetics, because agents marketed after 2008 (i.e., after the rosiglitazone saga) are not only required to reduce levels of HbA1c, but also to demonstrate beneficial or at least neutral effect with regard to cardiovascular (CV) outcomes (Figure 1). This is of paramount relevance, considering that the risk of developing CV disease is two-fold higher in patients with diabetes compared with individuals without diabetes [1]. Thus, pharmacovigilance is gaining a crucial role in guiding research and supporting clinical practice.



**Figure 1:** Evolving concepts in the perception (i.e., research priority and clinical implications) of safety issues related to antidiabetic drugs. HF: Heart Failure; MI: Myocardial Infarction.

Therefore, CV safety in patients with type 2 diabetes mellitus (T2DM) has recently gained an outstanding importance and dedicated clinical trials were designed, especially for most recent anti-diabetic classes. Among the published studies, TECOS, EXAMINE and SAVOR-TIMI addressed the CV safety of dipeptidyl peptidase 4 (DPP4) inhibitors (known as gliptins); ELIXA and LEADER analysed CV outcomes of lixisenatide and liraglutide (GLP-1 agonists), respectively; EMPA-REG-OUTCOME investigated the CV effect of empagliflozin, belonging to the latest pharmacological class of gliptins, inhibiting the renal sodium-glucose transporter 2 (SGLT-2) (Table 1).

As regards incretin-based therapy, the risk-benefit profile is well established: incretin treatment carries a low risk of hypoglycaemia, but

a mildly increased incidence of pancreatitis [2]. As to CV effects, a higher rate of hospitalization for heart failure (HF) emerged for some agents: SAVOR-TIMI reported an unexpected increase in the risk of HF in patients treated with saxagliptin compared to placebo; the increase in HF was higher in the first year of treatment and in patients with other risk factors for HF. In the EXAMINE trial, no statistically significant differences for the primary CV endpoint were demonstrated between alogliptin and placebo groups, although a trend for HF hospitalization was observed in patients with recent acute coronary syndrome [3]. Finally, TECOS documented no increased risk of CV outcomes and HF for sitagliptin, in keeping with possible drug specificity. This is an example of a pragmatic trial focused on CV outcomes in patients at risk of CV events in the setting of glycaemic equipoise, in order to limit biases related to different glycaemic levels [4].

Also data on gliptins are accruing. The results of the EMPA-REG-OUTCOME trial attracted a lot of interest because of the unanticipated large CV benefit: with the exception of UKPDS with metformin, in fact, all large trials aimed at better glucose control failed to show a remarkable improvement in CV outcomes. Patients treated with empagliflozin had significantly lower rate of the primary endpoint (MACE=composite of CV death, non-fatal myocardial infarction or stroke); CV death, non-fatal myocardial infarction or stroke occurred in 10.5% of the pooled treated group vs. 12.1% of the placebo group [3,5]. An unresolved issue regards the underlying mechanism implicated in reduced CV and total mortality, in the absence of significant decrease in myocardial infarction and death: beyond the documented reduction of blood pressure, it is likely that additional hemodynamic and/or metabolic effects are involved. Moreover, it is still unclear whether or not a class effect actually exists or, conversely, may be specifically attributed to the pharmacological properties of empagliflozin, showing higher selectivity on SGLT-2 cotransporter (IC50 for SGLT-2=3.1 vs. IC50 for SGLT-1=8,300) [6]. Results of similar studies conducted with dapagliflozin (DECLARE-TIMI58) and canagliflozin (CANVAS) will be available in 2019 and 2017, respectively, and will clarify this issue.

Within the CV issue, an additional unresolved aspect regards the generalizability of results to patients with lower CV risk and the persistence of the CV benefit (for empagliflozin) in the long-term, considering that all these studies have a limited duration (maximum 3 years); longer follow-ups are mandatory to evaluate all the aspects of progression of micro-vascular and macro-vascular damage related to glycaemic control.

	SAVOR-TIMI 53	EXAMINE	TECOS	ELIXA	LEADER	EMPAREG-OUTCOME
<b>Drug</b>	Saxagliptin	Alogliptin	Sitagliptin	Lixisenatide	Liraglutide	Empagliflozin
<b>Design</b>	Superiority	Non-inferiority	Non-inferiority	Non-inferiority	Non-inferiority	Non-inferiority
<b>n. patients</b>	16,492	5,380	14,671	6,068	9,340	7,028
<b>Population</b>	T2DM with pre-existing CVD or risk factors for CVD	T2DM with ACS within 15-90 days	T2DM with pre-existing CVD, <i>glycemic equipoise</i>	T2DM with ACS within 180 days, <i>glycemic equipoise</i>	T2DM aged ≥50 with at least one coexisting CVD	T2DM with established CVD, <i>glycemic equipoise</i>
<b>Follow up (median)</b>	2.1 years	1.5 years	3 years	2.1 years	3.8 years	3.1 years
<b>Baseline HbA1c (median)</b>	8	8	7.2	7.7	8.7	8.1
<b>Primary endpoint</b>	Composite of CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization or HF	Composite of death from CV causes, nonfatal MI, or nonfatal stroke	Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina	Composite of the first occurrence of death from CV causes, nonfatal MI, nonfatal	First occurrence of death from CV causes, nonfatal (including silent) MI, or nonfatal stroke	Composite of death from CV causes, nonfatal MI (excluding silent MI), or nonfatal stroke
<b>Secondary endpoints</b>	Hospitalization for HF, coronary revascularization, or unstable angina.	Urgent revascularization due to unstable angina within 24 h after hospital admission	First confirmed event of CV death, nonfatal MI, or nonfatal stroke; individual components of the primary composite outcome, including hospitalization for HF.	Composite of the primary endpoint or hospitalization for HF and a composite of the primary endpoint, hospitalization for heart failure, or coronary revascularization procedures	Expanded composite CV outcome (plus coronary revascularization, or hospitalization for unstable angina pectoris or HF), death from any cause, a composite renal and retinal microvascular outcome, neoplasms and pancreatitis	Composite of the primary outcome plus hospitalization for unstable angina
<b>Results</b>	<b>Superiority NOT ACHIEVED</b>	<b>Non-inferiority ACHIEVED</b>	<b>Non-inferiority ACHIEVED</b>	<b>Non-inferiority ACHIEVED</b>	<b>Non-inferiority ACHIEVED</b>	<b>Non-inferiority ACHIEVED</b>
	Primary endpoint: HR=1.03 (0.91-1.17).	Primary endpoint: HR=0.96 (upper boundary of the one-sided repeated CI=1.16).	Primary endpoint: HR=0.98 (0.89-1.08).	Primary endpoint: HR=1.02 (0.89-1.17)	Primary endpoint: HR=0.87 (0.78-0.97)	Primary endpoint: HR=0.86 (0.74-0.99)
	Hospitalization for HF: HR=1.27 (1.07-1.51)	Hospitalization for HF: HR=1.19 (0.89-1.89)	Hospitalization for HF: HR=1.00 (0.83-1.20)	Hospitalization for HF: HR=0.96 (0.75-1.23)	Hospitalization for HF: HR=0.87 (0.73-1.05)	Death from CV causes: HR=0.62 (0.49-0.77) Hospitalization for HF: HR=0.65 (0.50-0.85)

MI: Myocardial Infarction; HF: Heart Failure; CDV: Cardiovascular Disease; ACS: Acute Coronary Syndrome; T2DM: Type 2 Diabetes Mellitus; HR: Hazard Ratio (in parenthesis 95% confidence interval)

**Table 1:** Synopsis of published cardiovascular outcome trials.

From a safety standpoint, the harmful effects of gliflozins have been examined in many pre-approval trials. Predictable side effects are urinary tract infections (UTI) and genital infections (GTI), which are related to the mechanism of action of SGLT-2 inhibitors: increased and sustained glycosuria may facilitate the growth of microorganisms. UTIs occur in approximately 5% of gliflozin users, while GTIs occur in 5-10% of users, especially in females. All these adverse effects are generally mild or moderate and they all respond to standard antibiotics therapy; although few cases of pyelonephritis have been reported [6,7]. Hypovolemia is another possible predictable side effect related to the drug-related osmotic diuresis that may lead to volume depletion, reduced blood pressure and orthostatic hypotension; these conditions were more frequent in patients with predisposing factors such as elderly subjects, patients with moderate renal impairment or

concomitant treatment with loop diuretics. Fasting hypoglycaemia rare and possibly unrelated to gliflozins; it has been reported in patients with a co-administration of sulfonylurea or insulin.

Ketoacidosis and impaired kidney functions are debated adverse effects. As of May 2015, the Food and Drug Administration (FDA) received 73 cases of ketoacidosis in patients treated with gliflozins (reported in the FDA Adverse Event Reporting System - FAERS - database). The peculiarity of event is that nearly all cases were associated with normal blood glucose levels: for this reason it has been named "euglycaemic ketoacidosis". This condition is mostly associated with triggering factors such as infections, surgical procedure, trauma, reduced food and fluid intake. Besides, it could be associated with gliflozins related hyperglucagonemia which could be responsible for a

higher hepatic ketone production, hypovolemia and frequent infections [7,8].

The relationship between gliflozins and renal impairment is still uncertain: in clinical studies increased serum creatinine and reduction from baseline GFR were seen in 1–4% of gliflozin-treated patients. These changes were much larger in patients with previous moderate renal impairment (GFR<60 mL/min), in older patients (age>65) or in patients using diuretics. These effects were dose related and in most cases of mild/moderate intensity, with a return to previous baseline GFR after drug interruption. Acute reductions in GFR could be ascribed to hemodynamic effects (decrease in plasma volume and in blood pressure) or could be the consequence of tubule glomerular feedback due to increased delivery of sodium to the macula densa. This consequence might also be related to nephron glucotoxicity, linked to the mechanism of action of gliflozins [9]. The FDA also received 101 cases of acute kidney injury with sufficient detail to confirm the diagnosis and demonstrate a temporal relationship with canagliflozin (73 patients) and dapagliflozin (28 patients): these data could be the starting point for further analysis that will delineate the renal consequences of long-term exposure to SGLT-2 inhibitors. Considering that renal function could be progressively impaired by poor glucose control, drug–drug interactions and regular monitoring of renal function are mandatory.

The final consideration regards the place in therapy of these drugs and the optimal combination and sequence in diabetes management, considering that current guidelines strongly advocate for tailored therapy. As for pioglitazone, the potential cardiovascular benefit from the proactive study must be balanced against the documented increase of bladder cancer risk, a controversial and not fully understood adverse reaction also reported with gliflozins (especially dapagliflozin) [10]. Accordingly, the current European summary of product characteristics does not recommend the association of SGLT-2 inhibitors with pioglitazone as a precautionary measure [11].

In conclusion, there is a key role for pharmacovigilance in the era of CV outcomes trials of novel anti-diabetic drugs: the present uncertainty on their overall risk/benefit profile, especially the newer pharmacological class of gliflozins, calls for data coming from post-

authorisation safety studies (e.g., spontaneous reporting system and analytical observational studies) in order to guarantee the full characterisation of the CV effects as well as other rare safety issues. We also need to clarify the mechanism of action of gliflozins in renal tubules, as well as in all other organs where SGLT are expressed in order to better predict and understand side effects. This might help to define the optimal therapeutic strategy, once all pros and cons of anti-diabetic drugs are clarified.

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